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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Please do not complete any field with "not applicable" or n/a. Refer to the help text for what text to use if an item is not relevant to your study.
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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☒	☐	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used to collect data.
Data analysis	All code used to analyze and produce the results can be found in the referenced main github repository (https://github.com/almaan/stereoscope), it has also been deposited at Zenodo (doi : 10.5281/zenodo.3951884). Code for the method DWLS was accessed at https://github.com/dtsoucas/DWLS (with a slightly modified version, due to bugs) uploaded to the main (Stereoscope) github repository. Code for deconvSeq was accessed at https://github.com/rosedu1/deconvSeq.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Links to publicly available datasets:

Spatial Data:
Human Developmental Heart (ST1K): https://www.spatialresearch.org/resources-published-datasets/doi-10-1016-j-cell-2019-11-025/
Mouse Hippocampus (Visium) : https://support.10xgenomics.com/spatial-gene-expression/datasets/1.0.0/V1_Adult_Mouse_Brain
Mouse Hippocampus (Slide-seq) : https://singlecell.broadinstitute.org/single_cell/study/SCP354/slide-seq-study (Puck ID : 180413_7)
Mouse Cerebelllum (Slide-seq) : https://singlecell.broadinstitute.org/single_cell/study/SCP354/slide-seq-study (Puck ID : 180819 11)
Mouse Hippocampus (ST1K) : https://github.com/almaan/stereoscope/blob/master/data/mousebrain/mouse-st-data.zip (password : zNLXkYk3Q9znUseS)

Single Cell data:
Mouse Hippocampus : https://storage.googleapis.com/linnarsson-lab-loom/l1_hippocampus.loom
Mouse Cerebellum : https://storage.googleapis.com/linnarsson-lab-loom/l1_cerebellum.loom
Human Developmental Heart : https://www.spatialresearch.org/resources-published-datasets/doi-10-1016-j-cell-2019-11-025/

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Only publicly available data was used in the study. Hence, we did not construct the experimental design and/or decide on the number of individuals by which the data was sampled nor the number of data points collected for each sample.
Data exclusions	We did not actively exclude any datasets. The single cell data was at times subsampled, to reduce computational cost, when implemented this was done by randomly sampling cells from each annotated cell type (see Methods). In the array based spatial data (ST1K and Visium), only spots under the tissue were used. All beads with non-zero counts were included in the Slide-seq analysis.
Replication	See field "Sample size". We show reproducibility by using data from multiple technical platforms (ST1K, Visium and Slide-seq), as well as replicates for one of these instances (ST1K).
Randomization	See field "Sample size". We are not assessing effect size in association to an intervention or similar. Randomization is of no relevancy to our work.
Blinding	See field "Randomization".

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging